

# Glycosylation, Hypogammaglobulinemia and Resistance to Viral Infections

Demystifying Medicine  
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# UDP, 2 Affected Siblings

- Brother (Matthew, 11 yo)
  - Dysmorphic facial features
  - Global Developmental Delay
  - Spastic Paraparesis
  - Truncal Hypotonia
  - Bilateral Hearing Loss
  - Optic Atrophy
  - Cerebral atrophy, small corpus callosum, low NAA
  - Multiple Fractures
  - Hypo/agammaglobulinemia
- Sister (Ilia, 6 yo)
  - Dysmorphic facial features
  - Profound Global Developmental Delay
  - Generalized Hypotonia
  - Neonatal Seizures
  - Optic Atrophy
  - Cerebral atrophy, small corpus callosum, low NAA
  - Chronic Constipation
  - Hypo/agammaglobulinemia

# UDP, 2 Affected Siblings

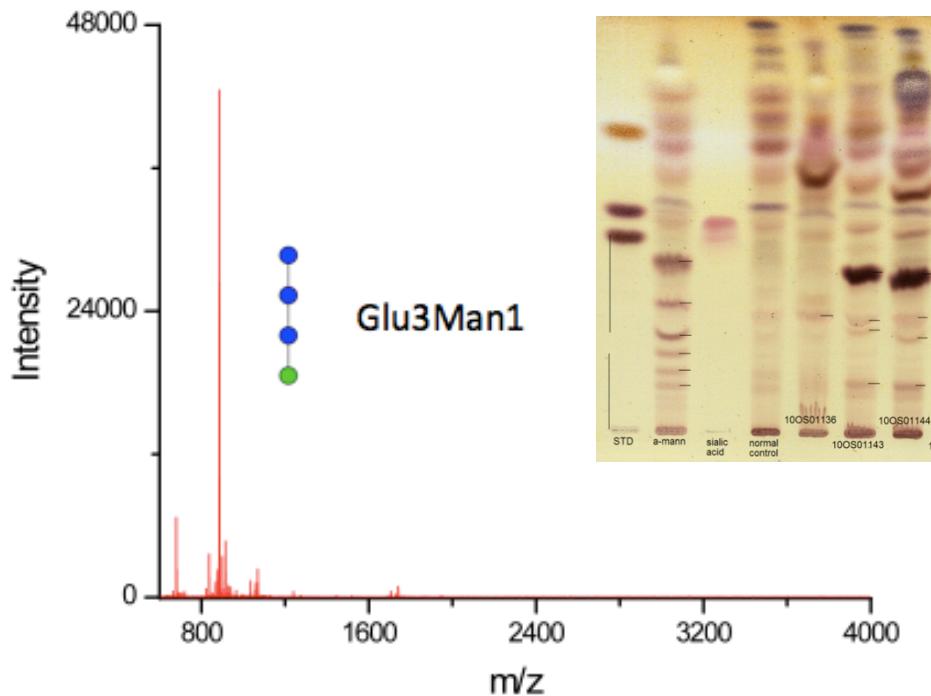


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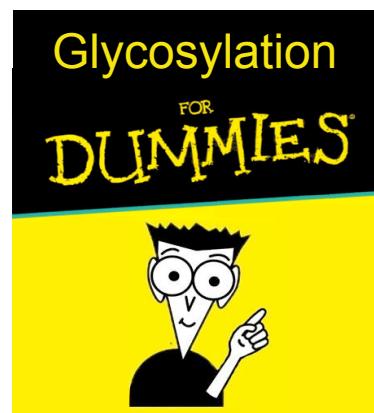
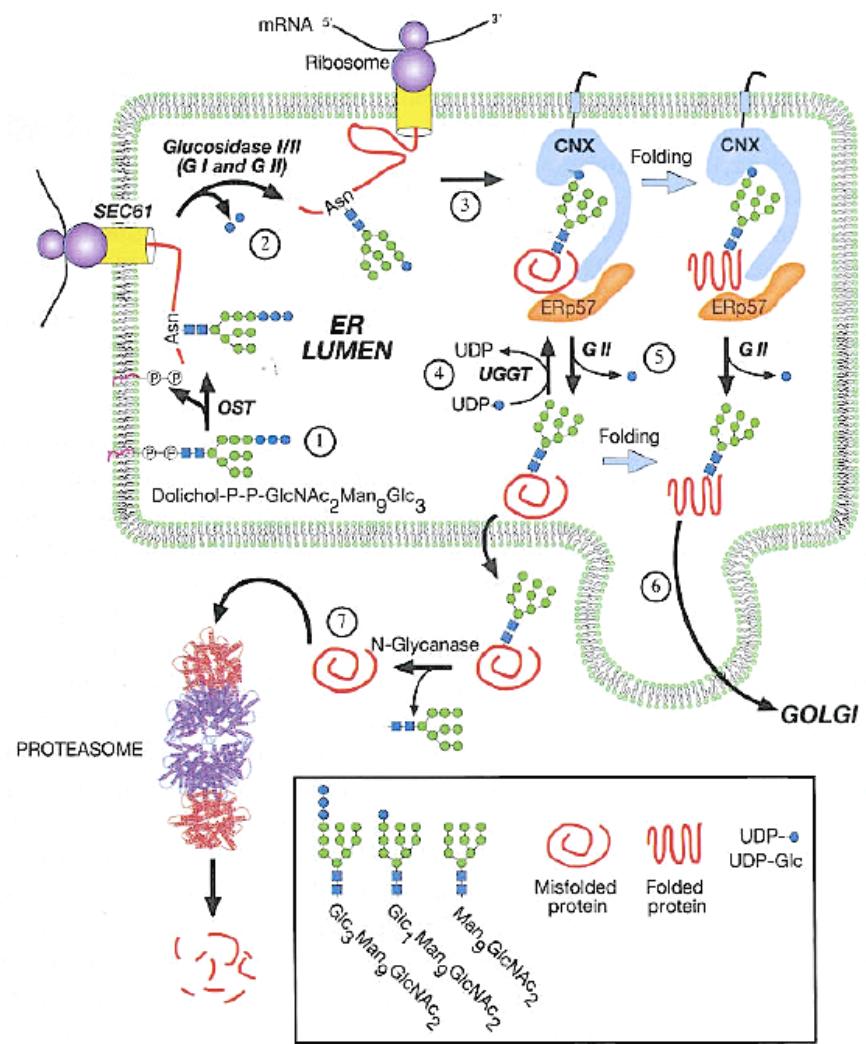
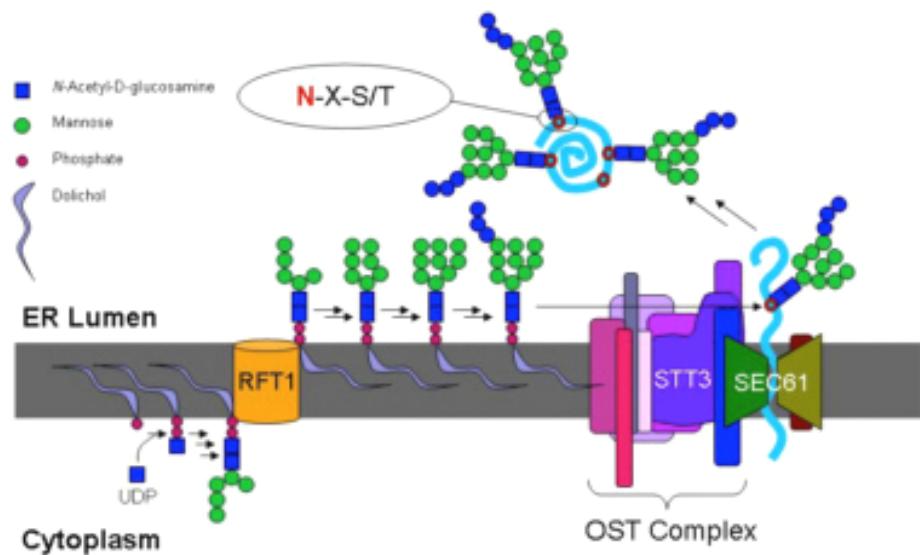
# UDP, 2 Affected Siblings



- CDG evaluation
  - Normal Serum Carbohydrate Deficient Transferrin
  - Abnormal urine thin layer chromatography
  - Abnormal urine MALDI-TOF

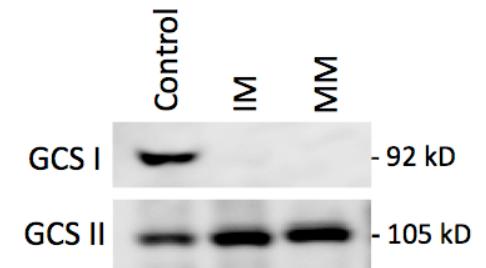


# N-Glycosylation and protein quality control



# UDP, 2 Affected Siblings

- Gene: *GCS1/MOGS* (CDGIIb)
  - Pat: c.65C>A, p.A22E; c.329G>A, p.110R>H
  - Mat: c.370C>T, p.124Q>X
- Protein/Enzyme defect:  $\alpha$ -glucosidase-I, responsible for glucose trimming as part of protein quality control.
- Prevalence: 1 case report (2000)  
36 week gestation, dysmorphic facial features, hypotonia, seizures, hepatomegaly, feeding problems, hypoventilation and death at 74 day



# UDP, 2 Affected Siblings



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  - **Hypo/agammaglobulinemia**

# PID-C->UDP, 2 Affected Siblings

- Albumin 4.2 gr/dL
  - IgG 142 (504-1465 mg/dL)
  - IgA 18 (27-195 mg/dL)
  - IgM 25 (24-210 mg/dL)
  - IgE 8.9 (<90 IU/mL)
- Tetanus (+) protective titers
- Diphtheria (+) protective titers
- HiB (+) protective titers
- Pnemoc. (+) protective titers
- Measles (-) protective titers
- Mumps (-) protective titers
- Rubella (-) protective titers
- Varicella (-) protective titers
- WBC 12,700 (N13/L78/M7/E2/B0)
  - C3/C4/CH50 130/17/103
  - LPAs PHA 186,154 cpm
  - DHR Normal
  - Ly phenotype
- CD3 2,469 uL (65%)
- CD4 1,788 uL (47%)
- CD8 553 uL (15%)
- CD16-56 150 uL (4%)
- CD19 1,220 uL (32%)
- CD19/27 93uL (2.4%)
- CD19 IgM/D/G/A 1,115/1,124/45/22

# PID-C->UDP, 2 Affected Siblings

**Agammaglob.**



**Infections**

	Bacterial	Viral	Parasitic	Fungal	Mycobact
T cells	X	X	X	X	X
B cells	X	X			
NK/NKT cells		X			
PMN cells	X			X	
MN cells	X		X		X
Complement	X				

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# Hypo/agammaglobulinemia evaluation



- Plasma cells
- UPR (Unfolded protein response)
- ERAD (ER-associated degradation)
- Ex-vivo Iggs production

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Mott cells



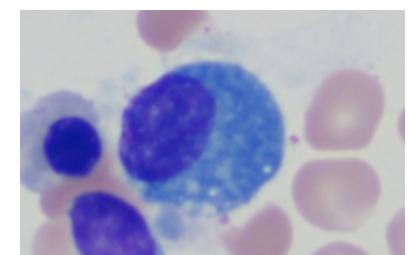
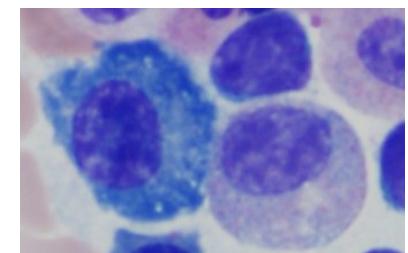
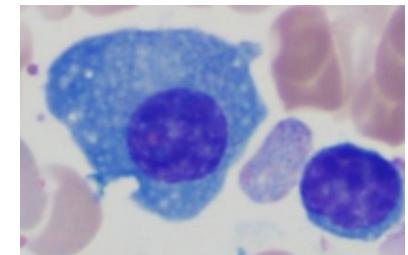
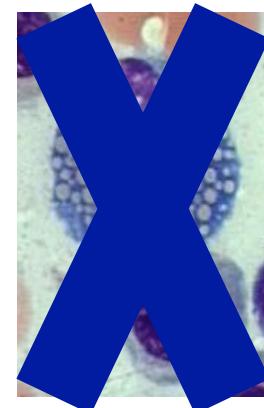
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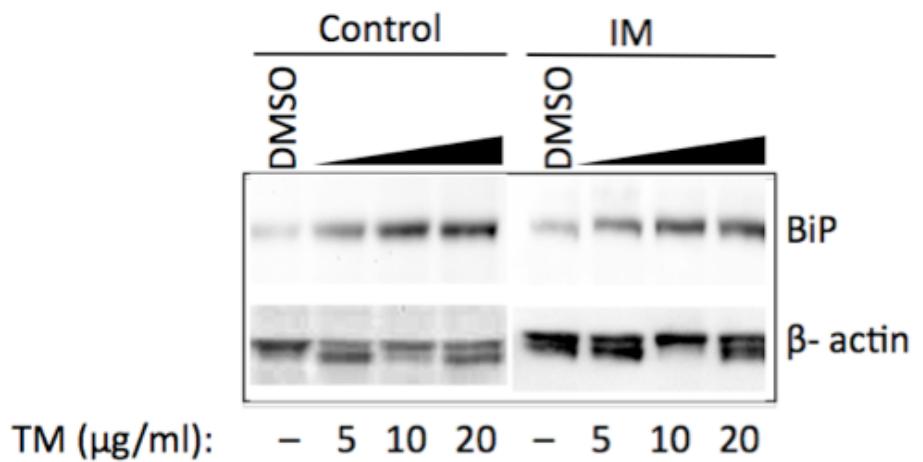


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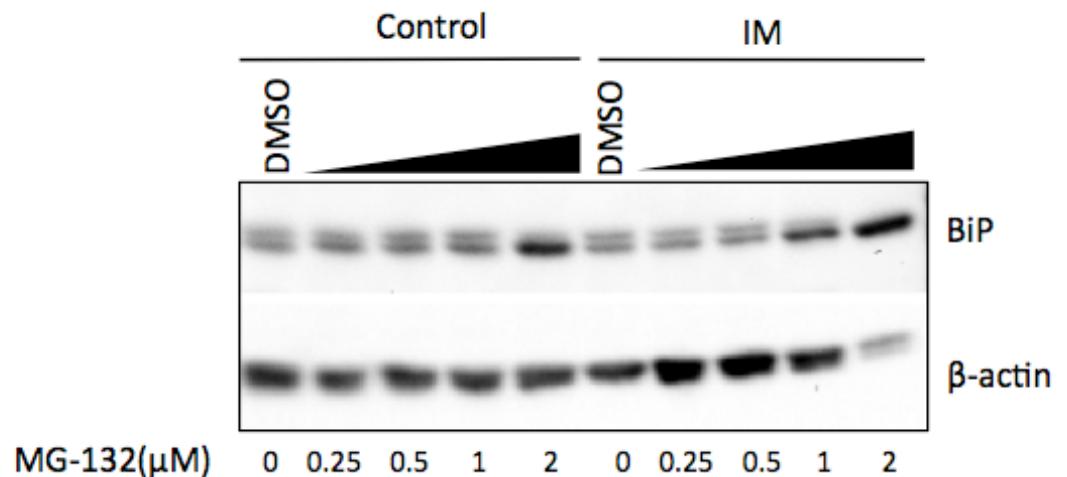


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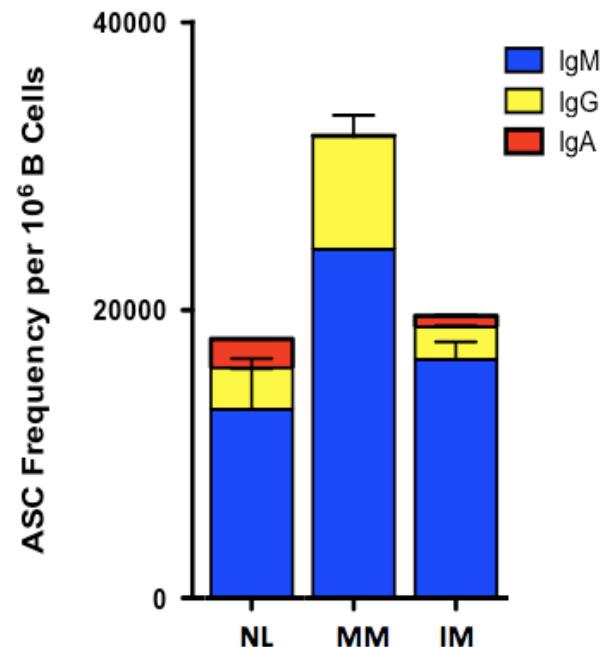


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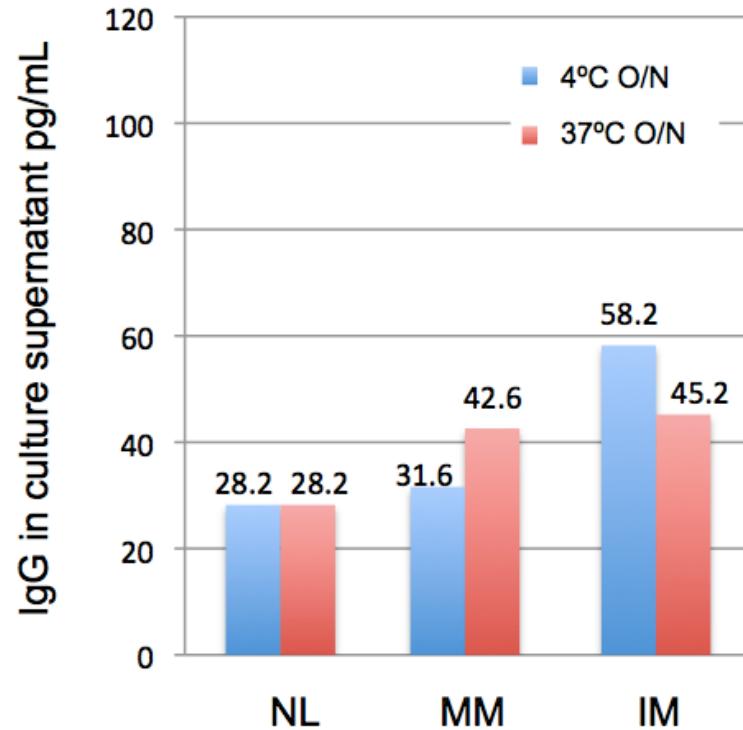


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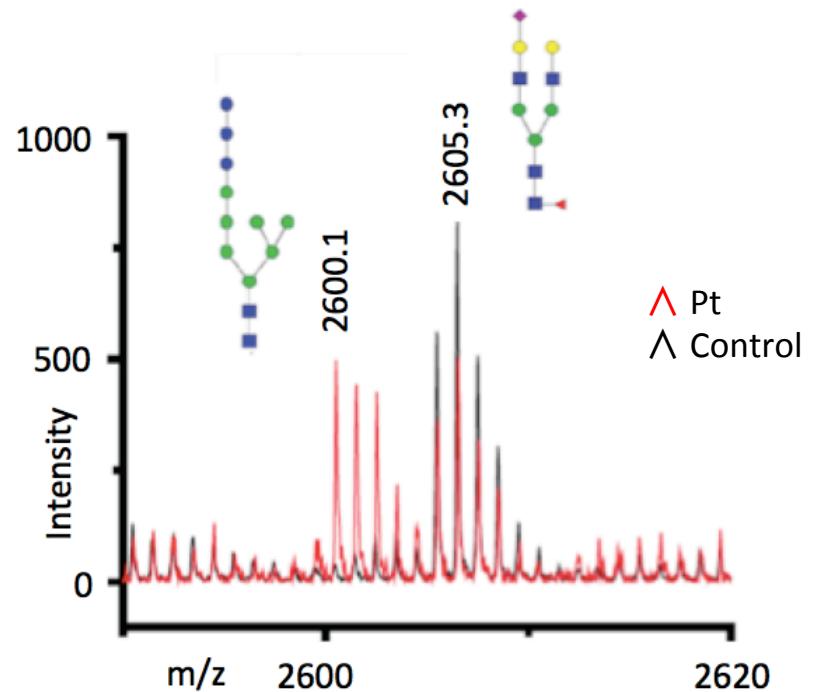


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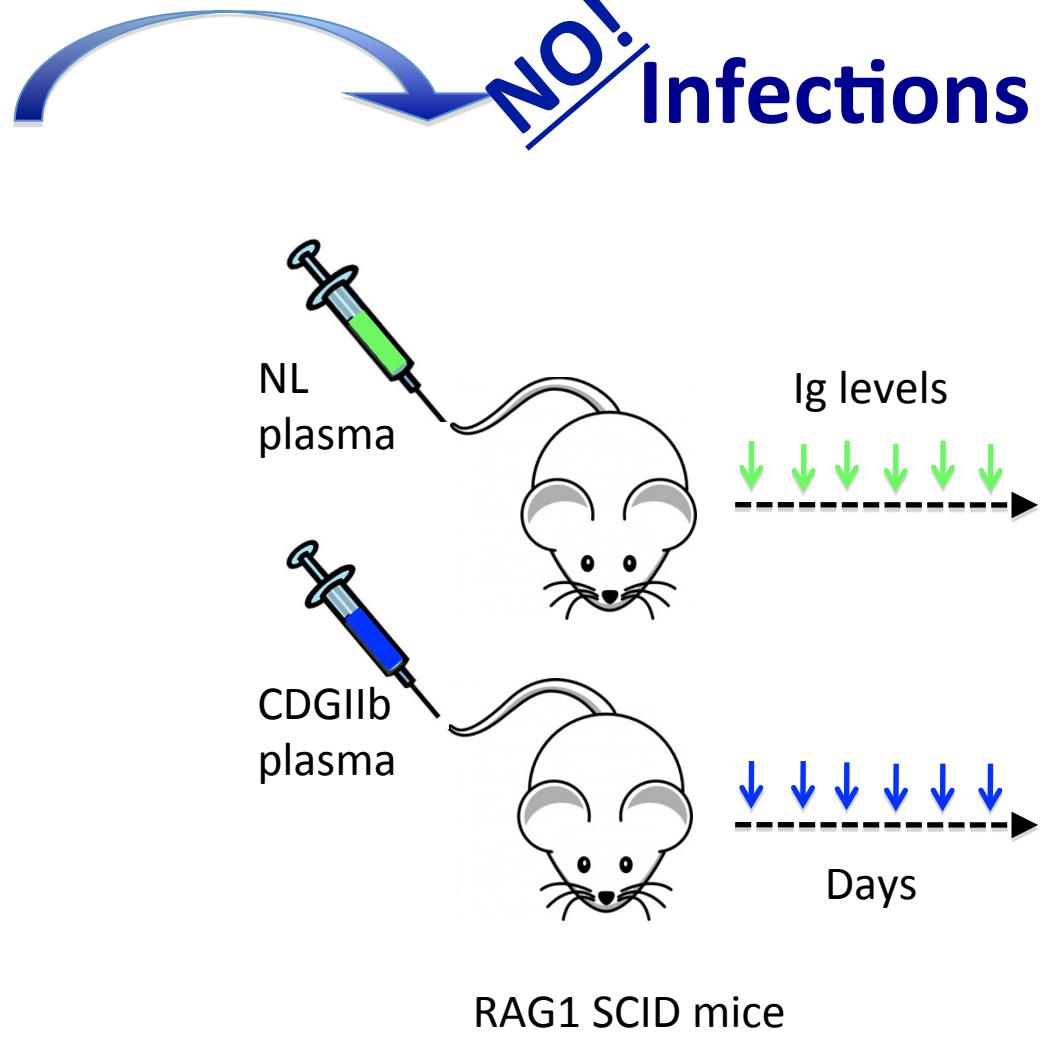


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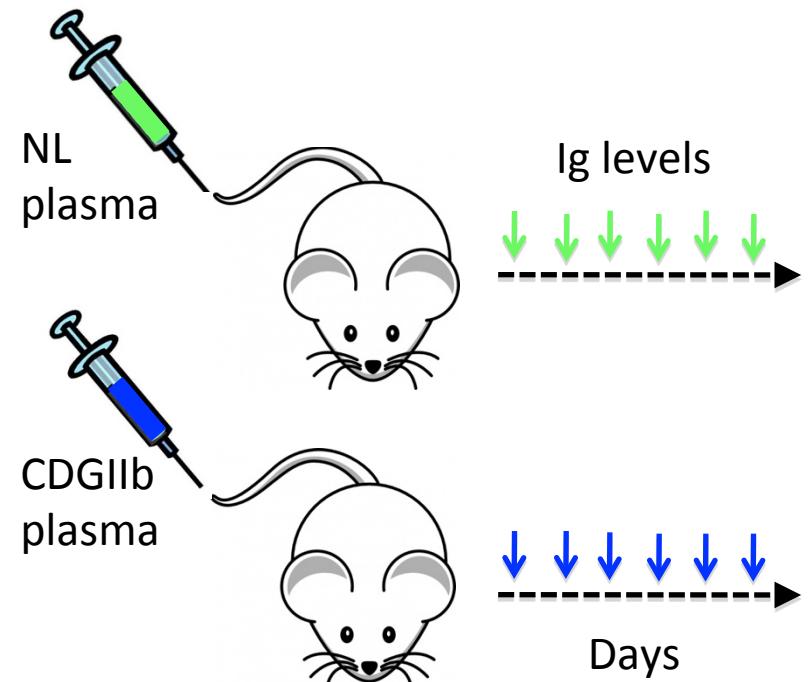
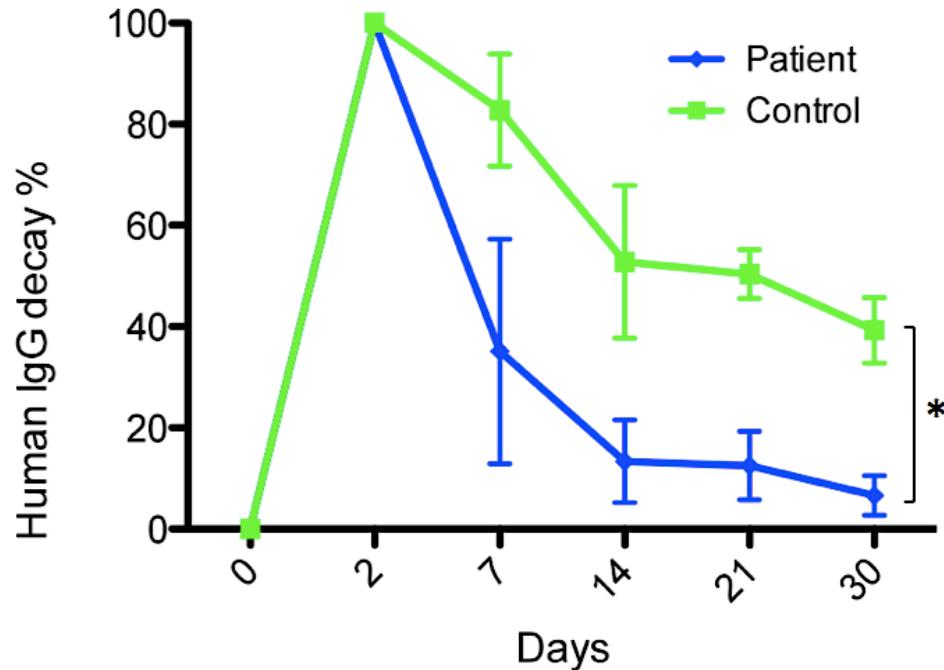
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- Ex-vivo Iggs production
- IgG half life



# Hypo/agammaglobulinemia evaluation

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- IgG half life

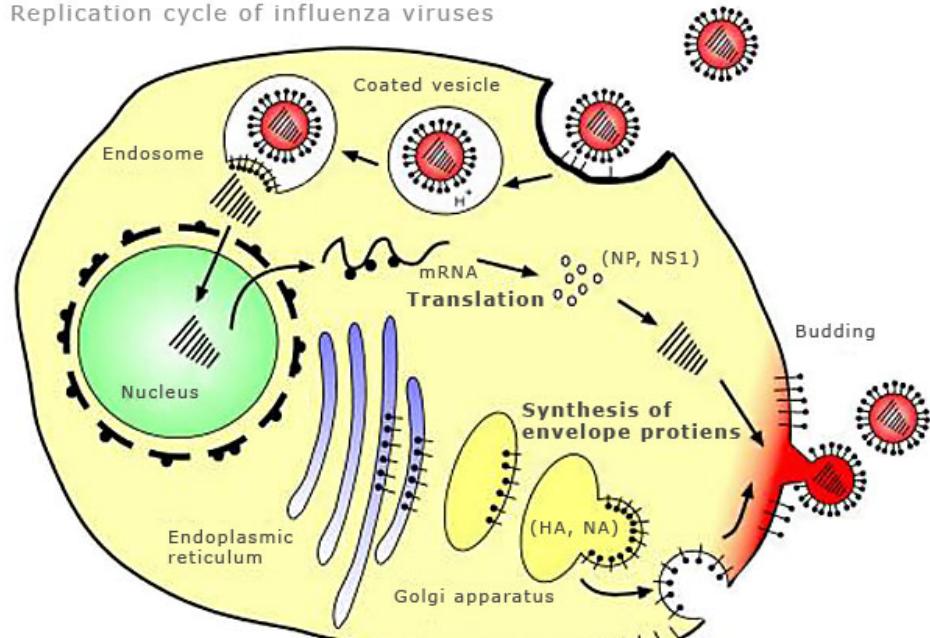
RAG1 SCID mice

# Viral susceptibility evaluation

Agammaglob.

**NO!** Infections

Replication cycle of influenza viruses



Courtesy of Influenza Report  
Reproduced by permission of Edward Arnold (Publishers) Ltd

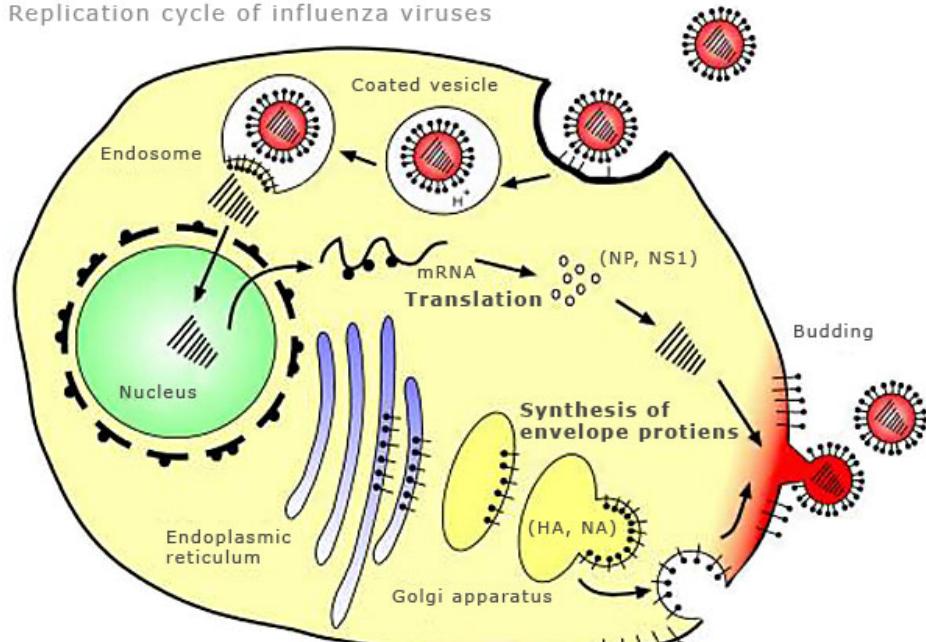
- Vaccinations and Titers
- |            |                          |
|------------|--------------------------|
| Tetanus    | -> (+) protective titers |
| Diphtheria | -> (+) protective titers |
| HiB        | -> (+) protective titers |
| Pnemoc.    | -> (+) protective titers |
| Measles    | -> (-) protective titers |
| Mumps      | -> (-) protective titers |
| Rubella    | -> (-) protective titers |
| Varicella  | -> (-) protective titers |

# Viral susceptibility evaluation

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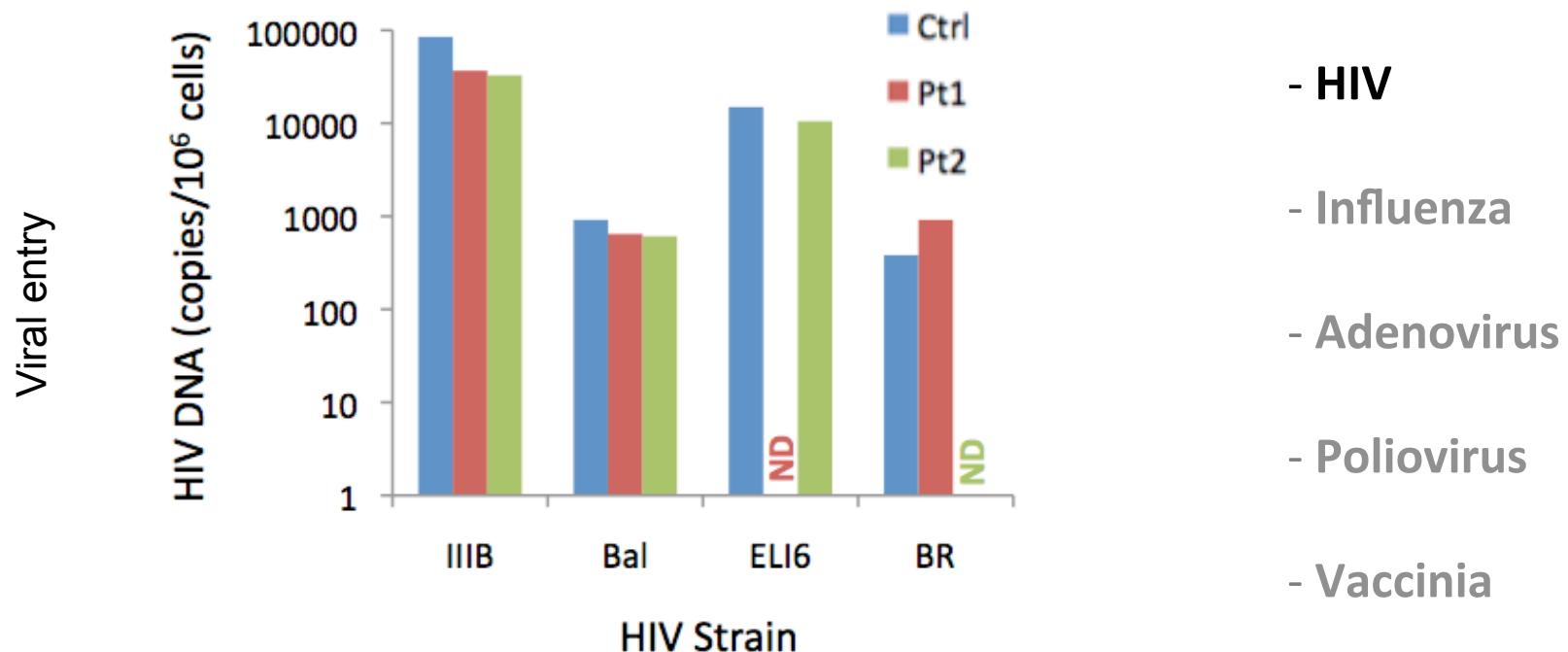
Replication cycle of influenza viruses



- HIV
- Influenza
- Adenovirus
- Poliovirus
- Vaccinia

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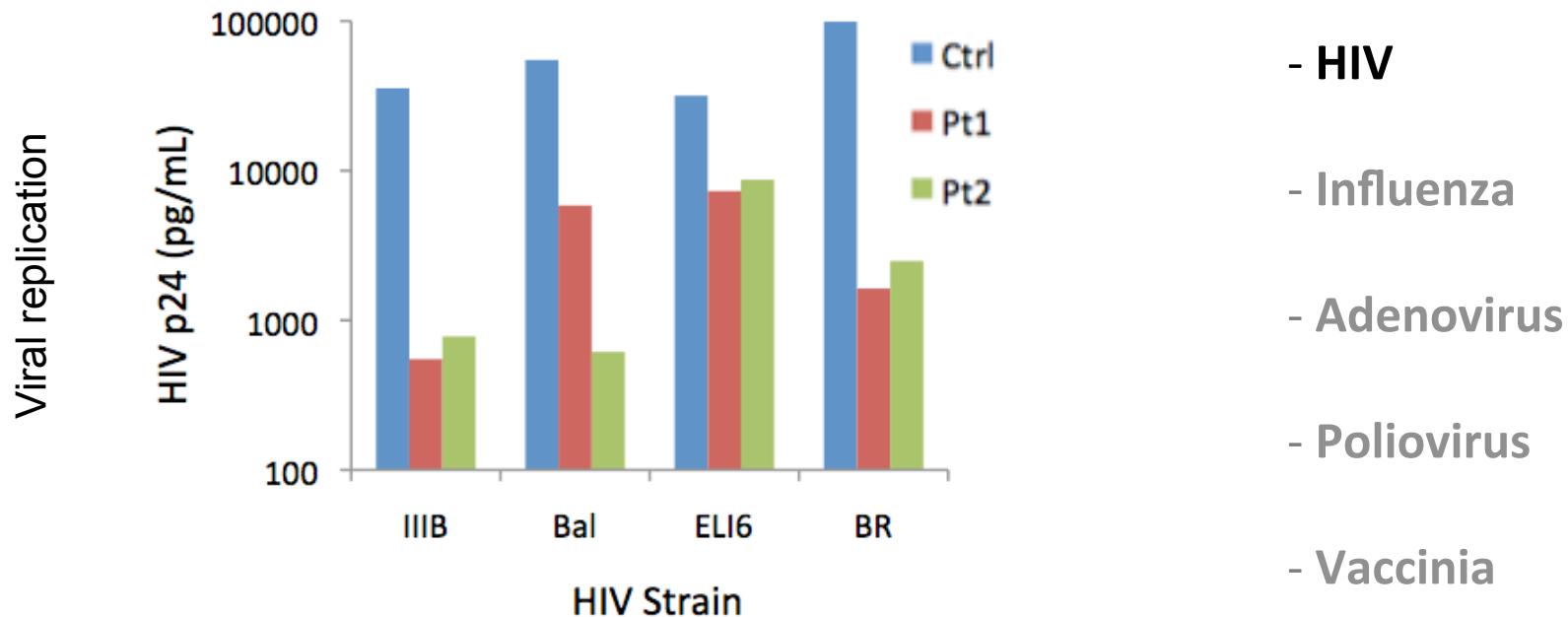
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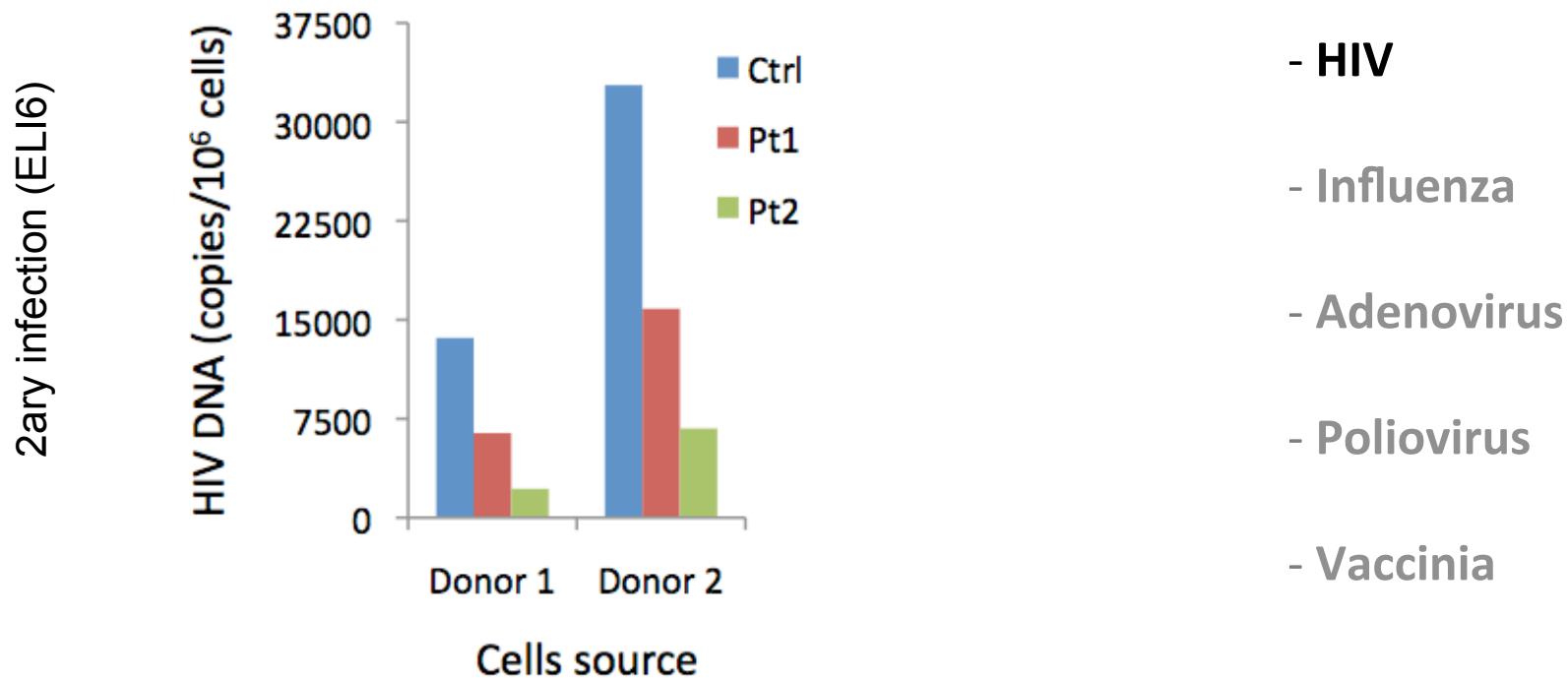
Agammaglob.

**NO!** Infections



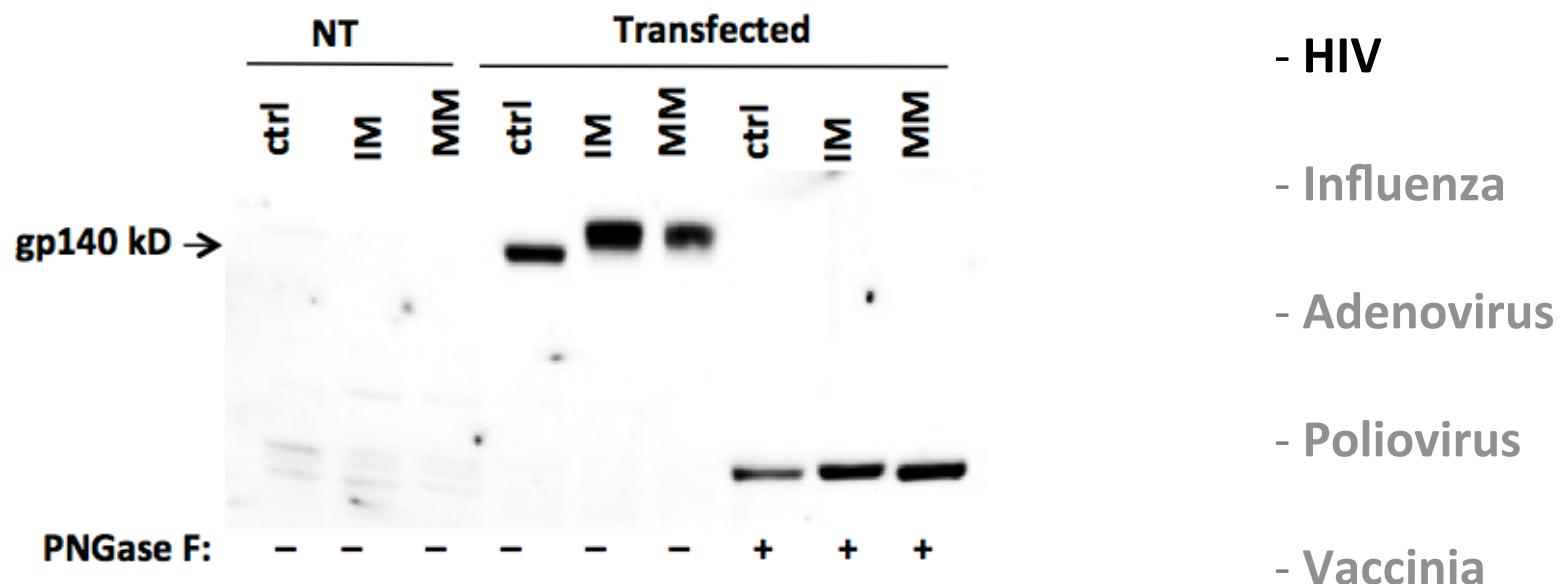
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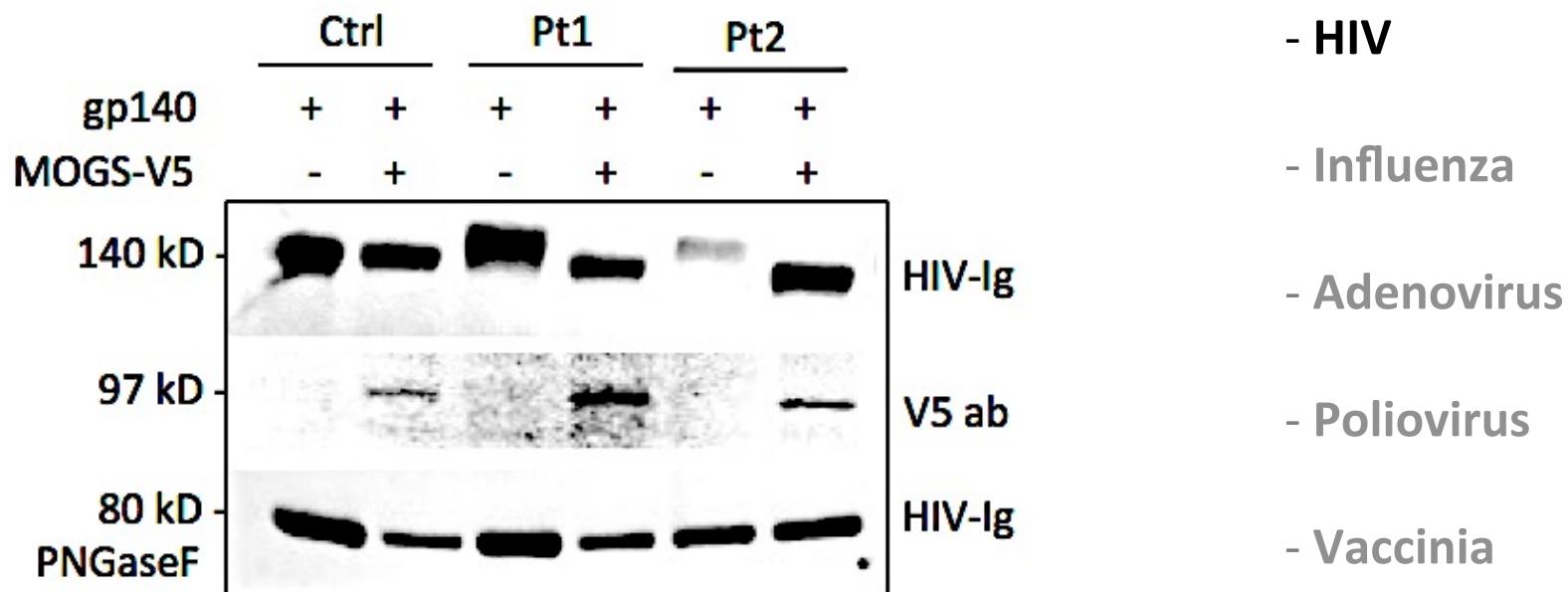
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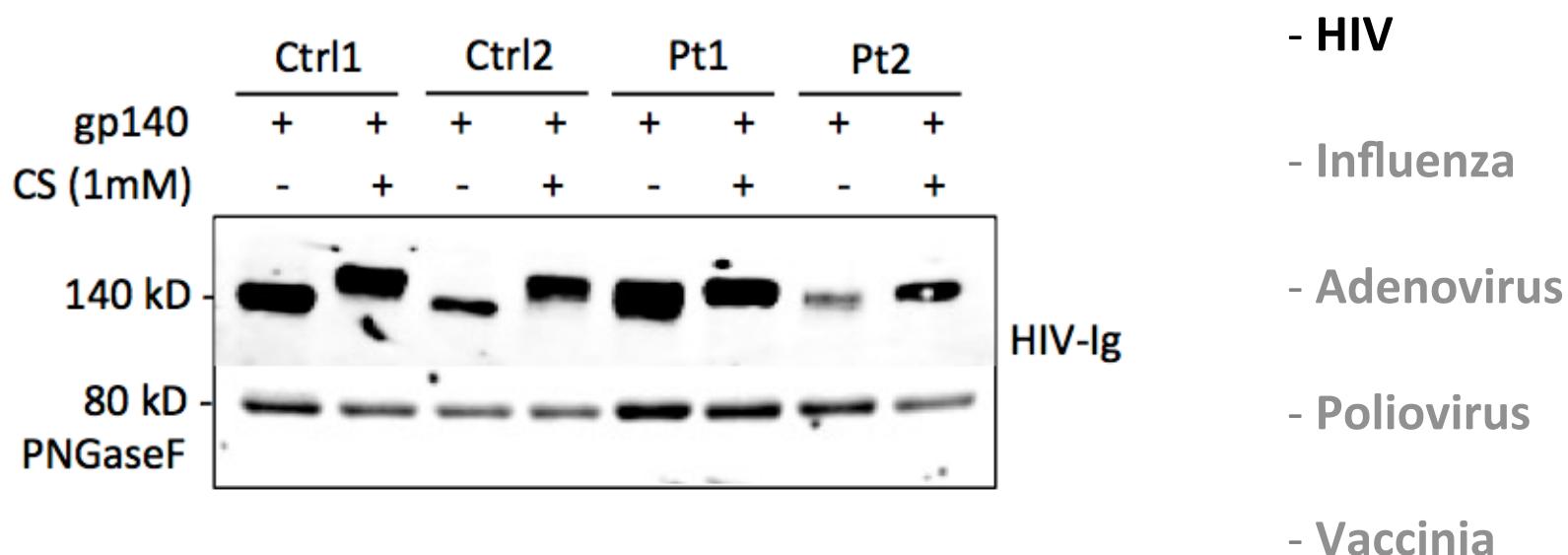
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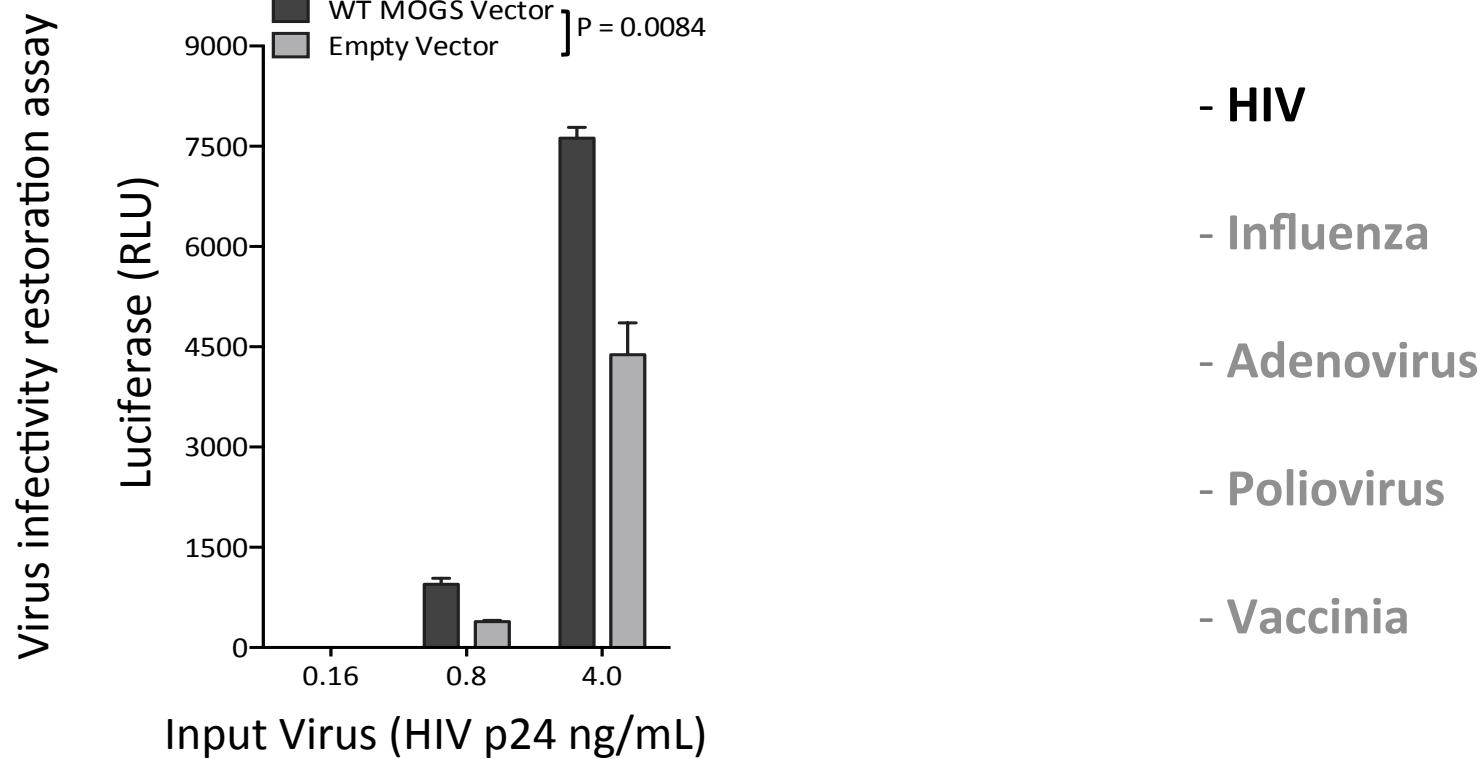
NO!  
Infections



# Viral susceptibility evaluation

Agammaglob.

NO!  
Infections



# Viral susceptibility evaluation

**Agammaglob.**



1ary infection

	MDM Culture 1		MDM Culture 2		MDM Culture 3	
	HA	TCID <sub>50</sub>	HA	TCID <sub>50</sub>	HA	TCID <sub>50</sub>
Patient 1	1:32	0.5×10	Neg	Neg	Neg	Neg
Patient 2	Neg	Neg	Neg	Neg	Neg	Neg
Control	1:64	2×10 <sup>2</sup>	1:64	2×10 <sup>2</sup>	1:64	2×10 <sup>2</sup>

- HIV

- Influenza

- Adenovirus

- Poliovirus

- Vaccinia

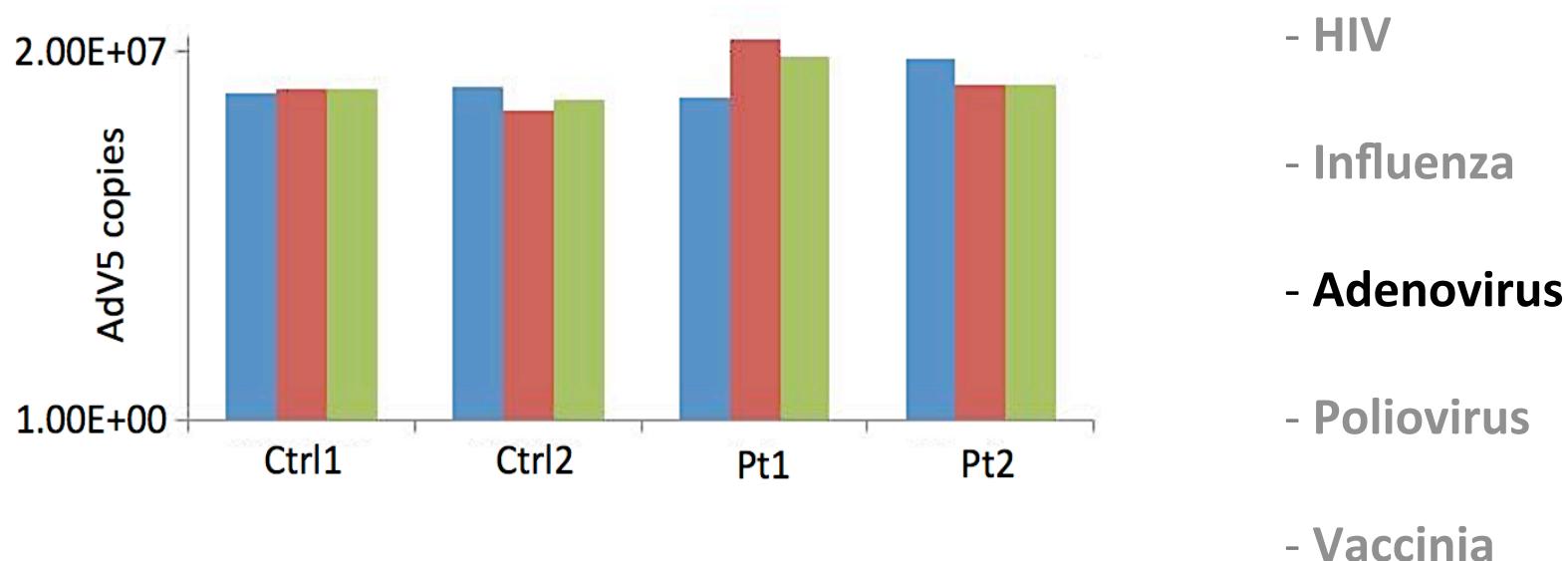
2ary infection

	MDCK Culture 1		MDCK Culture 2		MDCK Culture 3	
	HA	CPE	HA	CPE	HA	CPE
Patient 1	1:64	+/-	Neg	Neg	Neg	Neg
Control	1:32	+++	1:16	+++	1:16	+++

# Viral susceptibility evaluation

Agammaglob.

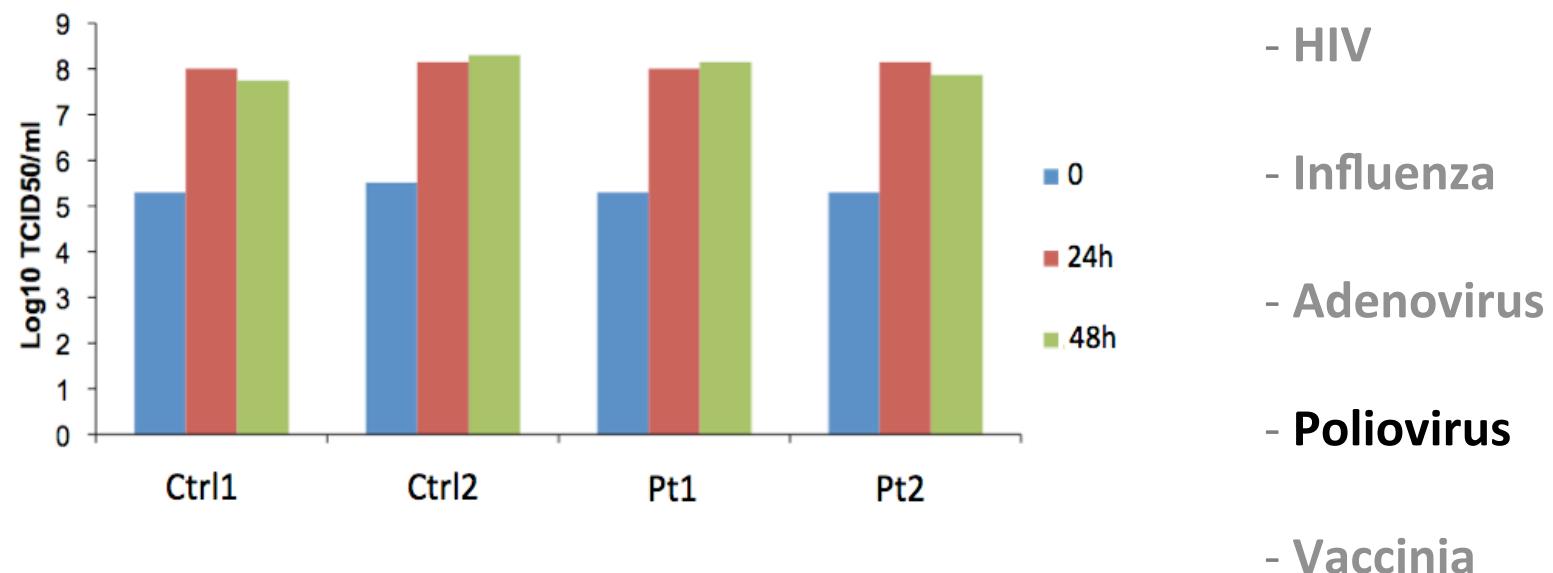
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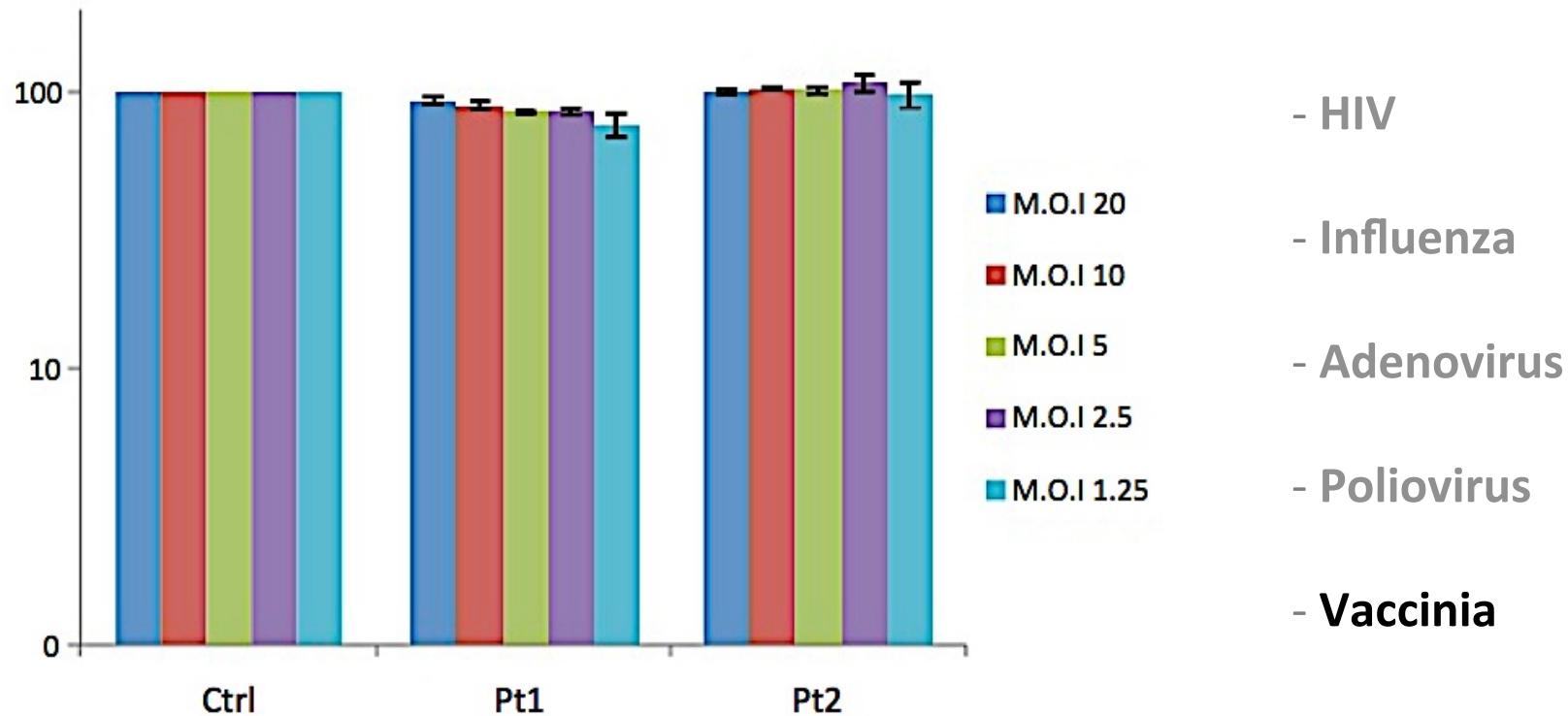
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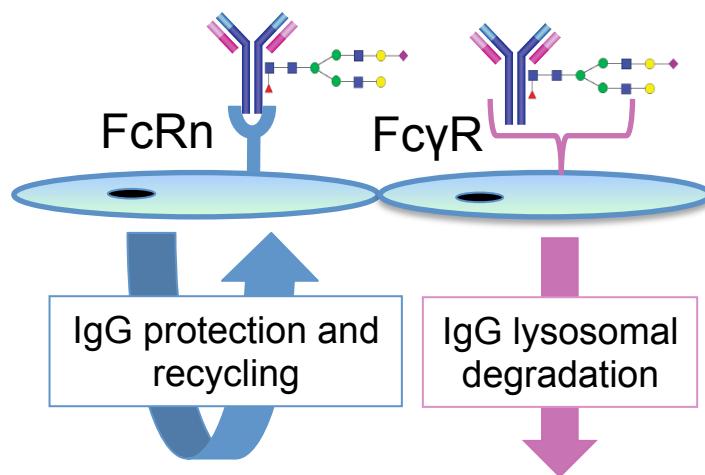
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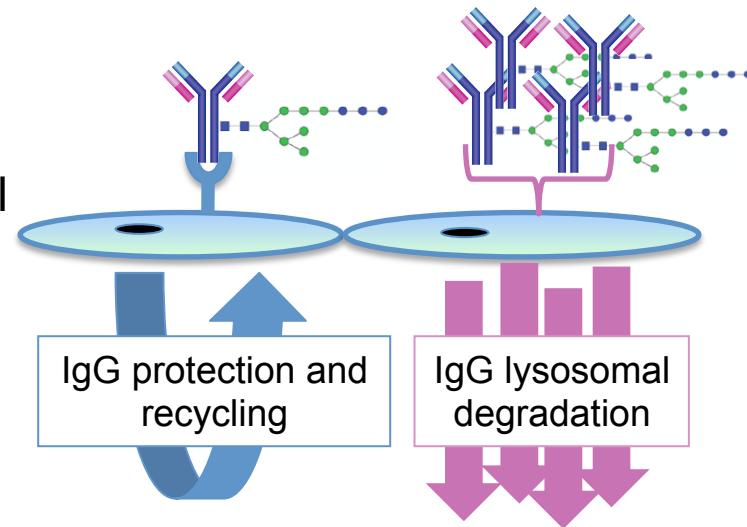
# Hypo/agammaglobulinemia model

WT glycosylated IgG



Normal  
IgG half life

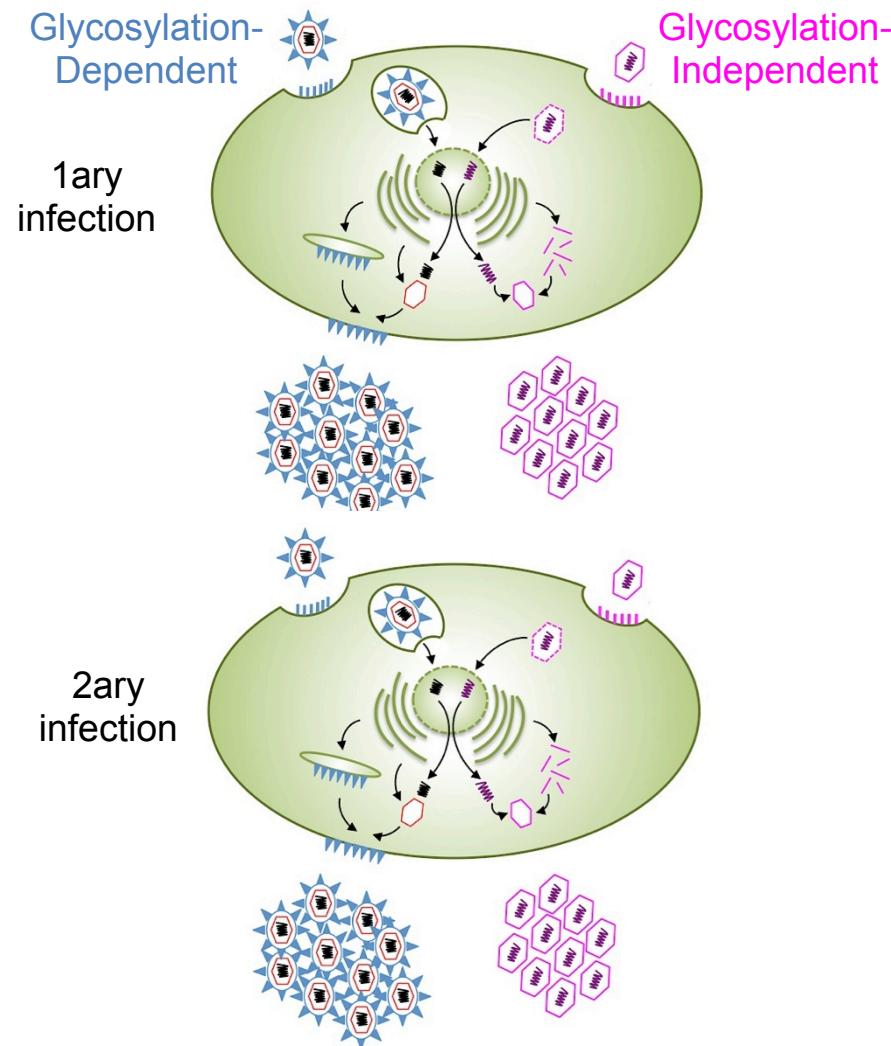
CDGIIb glycosylated IgG



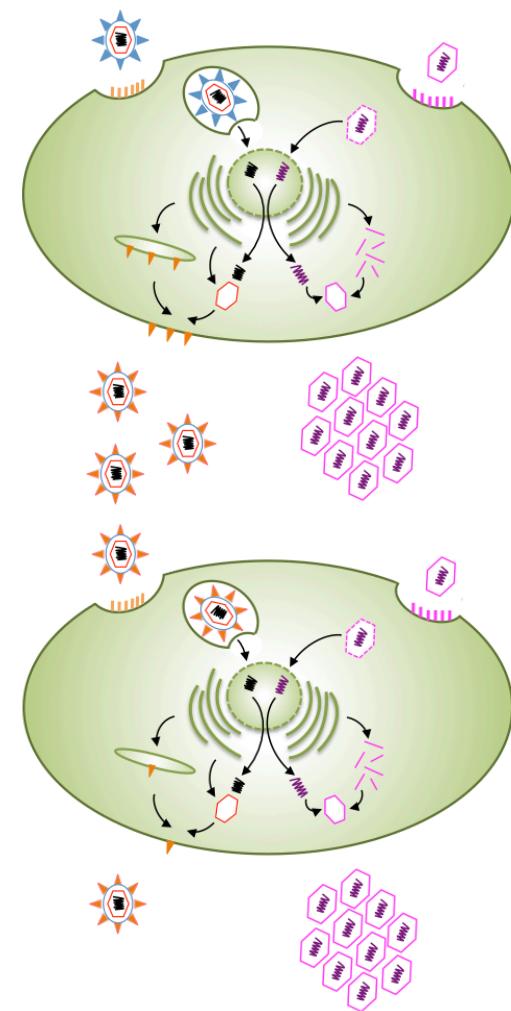
Shortened  
IgG half life

# Viral susceptibility model

Infections in WT cells



Infections in CDGIIb cells



# Acknowledgements

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-Jerome Jaques

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-Shakuntula Gurprasad

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-Warren Strober  
-Ivan Fuss

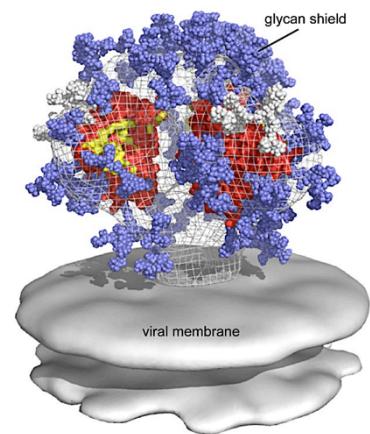
## **PID-C**

-Mary Garaofalo

# Viral susceptibility model



“It's the economy, stupid!” (circa, 1992)



“It's the virus, stupid!” (circa, 1995)



“It's the immune system, stupid!” (circa, 2010)

“It's the economy, AND the virus AND the immune system, AND the host, you people!” (circa, 2013)

